UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Offic
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

MJ

| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
|---|---|---|---|
| 09/129,298 | 08/05/98 | ARNTZEN C | 7991-023-999 |

HM12/1206

KIMERAGEN INC
300 PHEASANT RUN
NEWTOWN PA 18940

| EXAMINER | |
|---|---|
| ZAGHMOUT,O | |
| **ART UNIT** | **PAPER NUMBER** |
| 1638 | 12 |

**DATE MAILED:** 12/06/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

| Office Action Summary | Application No. 09/129,298 | Applicant(s) Arntzen et al. |
|---|---|---|
| | Examiner Ousama Zaghmout | Group Art Unit 1638 |

☒ Responsive to communication(s) filed on *amendment 09/15/2000.*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-4 and 8-27* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-4 and 8-27* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☒ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## STATUS OF APPLICATION

1. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. The amendment filed 09/15/2000 have been received and entered (Paper No. 10).

3. Status of the claims:

Claims 28-30, 50-53 have been canceled.

Claims 1-4, 8-27 are pending.

## Claim Rejections - 35 USC § 103

I. Claims 1-4, 8-27 are rejected under 35 U.S.C. § 103 as being unpatentable over Kmiec [Reference 1: US patent number: 5,565350. Date of publication: October 15, 1996] taken with Kmiec (Reference 2: US patent number: 5,731,181. Date of publication: March 24, 1998) and Stanford et al [US patent number: 5,204,253).

The claims are directed to a method of making a localized mutation in a target gene in a plant cell by adhering plant cells to a particle a recombinagenic oligonucleobase.

Kmiec et al teach a method for inducing alterations in targeted gene using recombinagenic oligonucleobase (Figure 1A and 1B) whereby a polynucleotide having both ribonucleotides and deoxyribonucleotides in a first strand and solely deoxyribonucleotides in a

second strand; wherein the strands are Watson-Crick paired and are linked by an oligonucleotide so that the polynucleotide has at most a single 3' and a single 5' end. Kmiec et al teach that these ends can be ligated so that the polynucleotide is a single continuous circular polymer (fourth paragraph, column 1). Kmiec et al teach that in order to effect a genetic change, there are within the region of homology one or more non-corresponding (hereinafter "heterologous" or "mutator") base pairs. Kmiec et al teach that the normal, constitutive cellular processes of homologous recombination cause the mutator nucleotides to be inserted into the targeted genomic site. The duplex oligonucleotides (hereinafter "chimeric vectors") can be used to alter specifically a gene of interest by introducing into the gene the heterologous base pairs. Kmiec et al teach that the heterologous base pairs can be base pairs different from the gene of interest, or base pairs in addition to those present in the gene of interest (an insertion), or, lastly, the heterologous base pairs can be the absence of base-pairs found in the gene of interest (a deletion). Kmiec et al teach this method is based on part on the discovery that the inclusion of a region of between about 15 and 50 base pairs of hybrid-duplex nucleic acid in the vector causes a greatly increased rate of alteration of the gene of interest. Kmiec et al teach that when the region of the heterologous base pairs is between 1 and 50 base pairs, the heterologous base pairs can be present in the vectors of the invention as either a homo-or a hybrid-duplex. Kmiec et al teach that when the heterologous base pairs are greater than 50 base pairs in length it is preferred that they be present as a homo-duplex. Kmiec et al teach that the vector can be introduced into the target cell by any method known to allow for the

introduction of nucleic acids into eukaryotic cells. Kmiec et al teach that without limitation as to theory, the chimeric vector is believed to be engaged by the recombination/repair mechanisms of the target cell and to direct a the alteration of the target gene by gene conversion or by homologous recombination (Column 3, lines 1-8 and column 4, lines 1-25). The reference teaches the transformation by electroporation (Example 6.2, columns 8 and 9).

Kmiec (reference 1) do not teach specifically of making the alteration in a plant cell.

Kmiec (reference 2) the the design and use of small, duplex oligonucleotides and oligomers of nucleotide analogs, termed Chimeric Mutational Vectors (CMV) to effect mutation in a target gene of a eukaryotic cell by homologous recombination between the CMV and the target. The CMV comprises ribonucleotides and deoxyribonucleotides and nucleotide analogs of each (generically "nucleobases"). The application discloses that CMV contain at least two segments of at least 3 ribo-type nucleobases paired to deoxyribo-type nucleobases, which regions flank the region of the CMV that corresponds to the mutation to be introduced into the target gene. Reference 2 further teach the uses of CMV in gene therapy of genetic diseases and construction of transgenic plants and animals (see at least the Abstract).

Stanford et al teach a method for transforming tobacco cells by particle-bombardment with the GUS marker gene (See Example 3, column 19 and 20)

Given the recognition of those of ordinary skill in the art of the value of a developing a method for correcting genetic diseases that are mainly controlled by a single point mutation or to develop a method for screening transgenic plant containing the desirable traits, it would have been obvious to one of ordinary skill in the art at the time the invention was made to incorporate the teaching of Kmiec (references 1 and 2) into the transformation process of Stanford et al, in order to produce a method for making localized mutation as claimed in the instant invention whereby said method can be used to correct genetic disorders in plants as suggested by Kmiec et al (reference 2, see at least Abstract). Furthermore, the number of bases used in the sequence of the homologous or intervening regions, the choice of gene used, the method of adhering and transformation are a matter of choice unless the proof of criticality is provided. Thus the claimed invention would have been prima facie obvious as a whole at the time it was made, especially in the absence of evidence to the contrary.

II. The rejection of Claims 1-4, 8-27 under 35 U.S.C. § 103 as being unpatentable over Kmiec et al [US patent number: 5,565,350 (the patent number was incorrectly cited as 5,731,181 in the previous Office action, this typographical error is regretted). Date of publication: October 15, 1996 (the date was correct in the last Office action] taken with Sanford et al [US patent number: 5, 204, 253; date of publication: April 20, 1993] has been

withdrawn in view of the new rejection described below. However, the Examiner have addressed the Applicants' argument as it pertains to the 103(a) stated below.

Applicants' arguments filed on 09/15/2000 have been carefully considered but not found to be persuasive.

A. applicants assert that the rejection under 35 USC § 103 is in error. Applicants point out that Kmiec does not explicitly disclose the transformation of plant cells with recombinagenic oligonucleobase using particle bombardment. Applicants further point out that Stanford teaches the transformation of cells, including plant cells, with plasmids, not recombinagenic oligonucleobase (paragraph 2 from the bottom, page 2 of the Remarks). This is not found persuasive for a number of reasons:

First: The references are relied upon in combination and are not meant to be considered separately as in a vacuum. It is the combination of all of the cited and relied upon references which make up the state of the art with regard to the claimed invention. Applicants' claimed invention fails to patentably distinguish over the state of the art represented by the cited references taken in combination. In re Young, 403 F.2d 754, 159 USPQ 725 (CCPA 1968); in re Keller 642 F. 2d 413, 208 USPQ 87 or possible improvements which applicants made. In re Scheckler, 438 F.2d 999, 10001, 168 USBQ 716, 717 (CCPA 1971). It is assumed that every reference relies to some extent on the knowledge of persons skilled in the art to complement that which is disclosed therein. Further, the skilled artisan is presumed to know something more about the art than only

what is disclosed in the applied references. In other words, the person having ordinary skill in the art has a level of knowledge apart from the content of the references. In re Bode, 550 F.2d 656,660,193 USPQ 12, 16, (CCPA 1977); In re Jacoby, 309 F. 2d 513, 516, 135 USPQ 317,319 (CCPA 1962). 1 (CCPA 1981). Therefore, as stated in the previous Office action, Kmiec et al teach a method for inducing alterations in targeted gene using recombinagenic oligonucleobase (Figure 1A and 1B) whereby a polynucleotide having both ribonucleotides and deoxyribonucleotides in a first strand and solely deoxyribonucleotides in a second strand. Kmiec et al further teach that the duplex oligonucleotides (hereinafter "chimeric vectors") can be used to alter specifically (emphasis added) a gene of interest by introducing into the gene the heterologous base pairs. The reference teaches the transformation by electroporation (Example 6.2, columns 8 and 9). Furthermore, those of ordinary skill in the art recognize that chimeric vector taught by the reference does contain an open reading frame linked to expression control sequences and origin of replication for replication of the plasmid in one or more cell types as encompassed by the claims of the instant invention. Kmiec teaches substantially the invention as claimed in a mammalian cell rather than in a plant cell. Those of ordinary skills in the art recognize that many of the genetic engineering procedures used in plant were first worked out in a mammalian cell. Examples of these are cloning, sequencing, transformation and many others. Hence, it would have been obvious for a person of ordinary skill in the art to modify the transformation system taught Stanford by incorporating the

chimeric vectors taught by Kmiec. The reasonable expectation of success would have been there as the mammalian genome is as complex as the plant genome and since it was shown to work in a mammalian cell, there is no doubt that it would not work if the same method is used in a plant cell. It is also important to mention that the electroporation method of delivering the gene into a cell has successfully been used in transforming plant cells from which transgenic plants were produced. Subsequently, making a localized mutation in a target cell in a plant does have the reasonable expectation of success, not as alleged by Applicants that is obvious to try only. Therefore, the rejection for obviousness is proper when the cited prior art references taken in combination to suggest the desirability of altering specifically (emphasis added) a gene of interest by introducing into the gene the heterologous base pairs.

B. Applicants assert that there is no reasonable expectation of success that the particle bombardment method of Sanford to allow for the successful making of a localized mutation in a desired gene in a plant cell (paragraph 1, page 3 of the Remarks). This is not found to be persuasive as Applicants have not provided any factual evidence to indicate that this would not be the case upon the transformation of a plant cell with recombinagenic oligonucleobase (Figure 1A and 1B) taught by Kmiec using the particle-bombardment as a method for delivery into a plant cell as taught by Stanford. Furthermore, the method as taught by Kmiec was successfully used in a making a localized mutation in a desired gene in the genome of mammalian cell which is as complicated as if not more than certain plant genome. Moreover, there was a suggestion in the prior art (e., 5,731,181) to use said method in gene therapy of

genetic diseases and construction of transgenic plants and animals (see at least the Abstract). In addition, all transformation methods including particle-bombardment and electroporation have been successfully used in the prior art to produce a stably transformed cell lines (plants or mammalian). Applicants have not provided the specific reason(s) why the combination of teachings of Kmiec and Stanford would not produce the invention as claimed in the instant application.

C. Applicants allege that the Examiner is using impermissible hindsight reconstruction based on knowledge of applicants' invention (second paragraph, page 3 of the Remarks). This is not found to be persuasive because the Examiner' decision was based on the finding that knowledge contained in the applicants' disclosure was also available from the prior art (i.e., it was available independently as discussed supra) at the time of the applicants' invention.

In light of the above, Examiner believes the prior art cited above does make the invention as claimed obvious. Therefore, the rejection of the pending claims is proper and should be maintained.

## Conclusion

No claims are allowed.

**Future Correspondence**

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Ousama M-Faiz Zaghmout whose telephone number is (703) 308-9438. The Examiner can normally be reached Monday through Friday from 7:30 am to 5:00 pm (EST).

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Paula Hutzell Ph.D., can be reached on (703) 308-4310. The fax phone number for the group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to THE MATRIX CUSTOMER SERVICE CENTER whose telephone number is (703) 308-0196.

Ousama M-Faiz Zaghmout Ph.D.

November 28, 2000

PAULA HUTZELL
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600